

A General Method for Convergent Synthesis of Polycyclic Ethers Based on Suzuki Cross-Coupling: Concise Synthesis of the ABCD Ring System of Ciguatoxin

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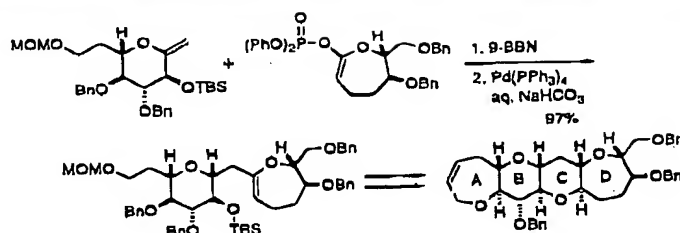
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ABSTRACT



A general method for convergent assembly of polyether structure has been developed based on palladium(0)-mediated Suzuki cross-coupling reaction of alkylboranes with cyclic ketene acetal phosphates. The present method allowed for coupling of medium-sized ether rings and thus a concise synthesis of the ABCD ring system of ciguatoxins has been achieved.

Marine polycyclic ethers, such as brevetoxins, ciguatoxins, and maitotoxin, present formidable and challenging synthetic targets due to their structural complexity and exceptionally potent biological activities.¹ One of the most critical issues in the synthesis of these large natural products is the development of synthetic methods for convergent coupling of polyether fragments. Despite recent advances in the synthesis of medium-sized cyclic ethers,² only a few methods for the convergent assembly of polyether structure have been reported to date.³ In connection with the synthetic studies on ciguatoxins,^{4,5} we have recently developed a new strategy

for convergent synthesis of polyether frameworks based on palladium(0)-catalyzed Suzuki cross-coupling of alkylboranes with cyclic ketene acetal triflates.^{6,7} Although this method has represented a powerful tool for the efficient construction of trans-fused polytetrahydropyran ring systems via coupling of six-membered rings, seven-membered ketene acetal triflates could not be utilized as the substrates in this coupling reaction due to their instability under the aqueous basic

(1) For recent reviews on ciguatoxins and related marine toxins, see (a) Yasumoto, T.; Murata, M. *Chem. Rev.* 1993, 93, 1897. (b) Scheuer, P. J. *Tetrahedron* 1994, 50, 3.

(2) For recent reviews on polyether synthesis, see (a) Alvarez, E.; Cundenas, M.-L.; Pérez, R.; Ravelo, J. L.; Martín, J. D. *Chem. Rev.* 1995, 95, 1953. (b) Mori, Y. *Chem. Eur. J.* 1997, 3, 849.

(3) (a) Nicolaou, K. C.; Prasad, C. V. C.; Hwang, C.-K.; Duggan, M. E.; Vesale, C. A. *J. Am. Chem. Soc.* 1989, 111, 5321. (b) Nicolaou, K. C.; Postema, M. H. D.; Claiborne, C. F. *J. Am. Chem. Soc.* 1996, 118, 1565. (c) Oishi, T.; Nagumo, Y.; Hiram, M. *Synlett* 1997, 980. (d) Oishi, T.; Nagumo, Y.; Hiram, M. *Chem. Commun.* 1998, 1041. (e) Nicolaou, K. C.; Gunzner, J. L.; Shi, G.-q.; Agrios, K. A.; Gärtner, P.; Yang, Z. *Chem. Eur. J.* 1999, 5, 646. (f) Very recently, the ABCDE ring framework of ciguatoxin has been prepared using alkylation-ring-closing metathesis approach; Macdu, K.; Oishi, T.; Oguri, H.; Hiram, M.; *Chem. Commun.* 1999, 1063.

1 (R = H) : CTX3C
2 (R = OH) : 51-HydroxyCTX3C

We chose to examine the cross-coupling of the alkylborane generated in situ via the hydroboration of *exo*-olefin **3**¹² with cyclic ketene acetal phosphate **4a**¹³ as a model system to establish the reaction conditions (eq 1, Table 1). Hydrobo-

(5) For recent synthetic studies from other groups, see (a) Oka, T.; Fujiwara, K.; Murai, A. *Tetrahedron* 1996, 52, 12091. (b) Oishi, T.; Shoji, M.; Maeda, K.; Kumahara, N.; Hirama, M. *Synlett* 1996, 1165. (c) Alvarez, E.; Delgado, M.; Díaz, M. T.; Hanning, L.; Pérez, R.; Martin, J. D. *Tetrahedron Lett.* 1996, 37, 2865. (d) Isobe, M.; Hosokawa, S.; Kira, K. *Chem. Lett.* 1996, 473. (e) Aitsuta, H.; Fujiwara, K.; Murai, A. *Synlett* 1997, 307. (f) Oishi, T.; Maeda, K.; Hirama, M. *Chem. Commun.* 1997, 1289. (g) Oguri, H.; Hishiyama, S.; Sato, O.; Oishi, T.; Hirama, M.; Murata, M.; Yasumoto, T.; Harada, N. *Tetrahedron* 1997, 53, 3057. (h) Oishi, T.; Shoji, M.; Kumahara, N.; Hirama, M. *Chem. Lett.* 1997, 845. (i) Oka, T.; Fujiwara, K.; Murai, A. *Tetrahedron Lett.* 1997, 38, 8053. (j) Ami, E.; Kishimoto, H.; Ohrai, H.; Meguro, H. *Biosci. Biotech. Biochem.* 1997, 61, 2019. (k) Oka, T.; Murai, A. *Tetrahedron* 1998, 54, 1. (l) Oka, T.; Fujiwara, K.; Murai, A. *Tetrahedron* 1998, 54, 21. (m) Oishi, T.; Nagumo, Y.; Hirama, M. *Chem. Commun.* 1998, 1041. (n) Isobe, M.; Nishizawa, R.; Hosokawa, S.; Nishikawa, T. *Chem. Commun.* 1998, 2665. (o) Hosokawa, S.; Isobe, M. *J. Org. Chem.* 1999, 64, 37. (p) Saeng, R.; Isobe, M. *Tetrahedron Lett.* 1999, 40, 1911. (q) Oguri, H.; Sasaki, S.; Oishi, T.; Hirama, M. *Tetrahedron Lett.* 1999, 40, 5405 and references therein.

(7) For a review on Suzuki cross-coupling reaction, see Miyaura, N.; Suzuki, A. *Chem. Rev.* 1995, 95, 2457.

(C) cyclic hetero acetal phosphates were successfully used for palladium-(O)-catalyzed Stille coupling, leading to the total synthesis of brevotoxin A. see (a) Nicolaou, K. C.; Shi, G. Q.; Gunzner, J. L.; Gärtner, P.; Yang, Z. *J. Am. Chem. Soc.* 1997, **119**, 5467. (b) Nicolaou, K. C.; Wallace, P. A.; Shi, S.; Ouellette, M. A.; Bunnage, M. E.; Gunzner, J. L.; Agrios, K. A.; Shi, G.-q.; Gärtner, P.; Yang, Z. *Chem. Eur. J.* 1999, **5**, 618.

(9) Very recently, nickel(0)- and palladium(0)-catalyzed Suzuki cross-coupling reactions of arylboronic acids with enol phosphates have been reported, see (a) Huffman, M. A.; Yasuda, N. *Synlett* 1999, 471. (b) Nan, Y.; Yang, Z. *Tetrahedron Lett.* 1999, 40, 3321.

Entry	Phosphate ^a	Product	% Yield
1 ^c			72
2 ^d			84
3			98
			87
4			
			97
5			
			94
6			
			96
7			
			98
8			

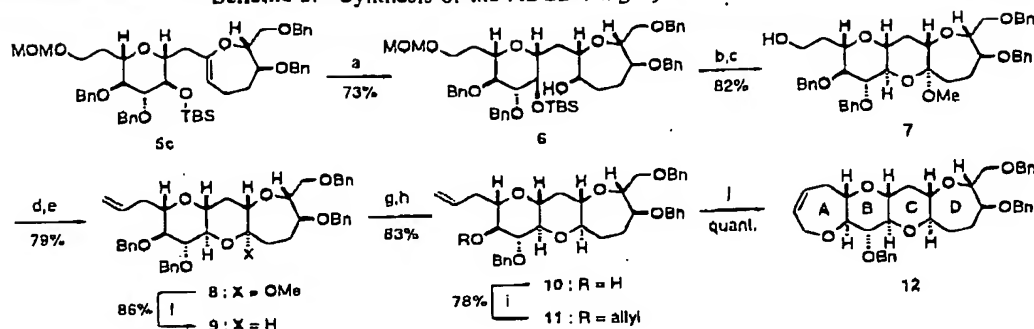
ration of **3** with 9-BBN (2.6 equiv, THF, r.t. to 60 °C) provided the corresponding alkylborane, which was in situ coupled with 1 equiv of **4a** under conventional Suzuki conditions [aqueous K_3PO_4 , $Pd(PPh_3)_4$, DMF] to yield the desired coupling product **5a** albeit in moderate yield (46–

(11) Satake, M.; Fukui, M.; Legrand, A.-M.; Cruchet, P.; Yasumoto, T. *Tetrahedron Lett.* 1998, 39, 1197.

(12) Synthetic scheme for compound 3 is included as Supporting Information.

(13) The ketene acetal phosphates were prepared from the corresponding lactones following the procedure of Nicolaou et al., see ref 8.

Scheme 1. Synthesis of the ABCD Ring System of CTX3C¹¹



^a Reagents and conditions: (a) Thexylborane, THF, $-20 \rightarrow 0^\circ\text{C}$, then H_2O_2 , NaOH; (b) $(\text{COCl})_2$, DMSO, Et_3N , CH_2Cl_2 , $-78^\circ\text{C} \rightarrow \text{r.t.}$; (c) TsOH , $\text{MeOH}-\text{CH}_2\text{Cl}_2$ (4:1), $\text{r.t.} \rightarrow 55^\circ\text{C}$; (d) $\text{SO}_3\cdot\text{Py}$, Et_3N , DMSO, CH_2Cl_2 , $0^\circ\text{C} \rightarrow \text{r.t.}$; (e) $\text{Ph}_3\text{P}^+\text{CH}_3\text{Br}^-$, NaHMDS, THF, 0°C ; (f) Et_3SiH , $\text{BF}_3\cdot\text{OEt}_2$, $\text{CH}_2\text{Cl}_2-\text{CH}_3\text{CN}$ (5:3), r.t. ; (g) I_2 , CH_2Cl_2 , $0^\circ\text{C} \rightarrow \text{r.t.}$; (h) Zn, AcOH, $\text{Et}_2\text{O}-\text{MeOH}$, r.t. ; (i) NaHMDS, allyl bromide, DMF, $0^\circ\text{C} \rightarrow \text{r.t.}$; (j) $\text{RuCl}_2(\text{=CHPh})(\text{PCy}_3)_2$, CH_2Cl_2 , r.t.

56%). Presumably, hydrolysis of 4a would occur competitively under these conditions due to the slow rate of oxidative addition of less reactive 4a to the palladium(0) complex. The yield of 5a was improved by carrying out the reaction with aqueous NaHCO_3 as a milder base instead of K_3PO_4 (Table 1, entry 1). Finally, the best result was obtained when excess 4a (2 equiv) was employed, giving 5a in nearly quantitative yield (entry 3). Other phosphine-free palladium catalysts such as $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$ proved ineffective, which is consistent with the results of cross-coupling of phenylboronic acid with an enol phosphate.^{9a}

It is noteworthy that this coupling reaction can be applied to not only six-membered ketene acetal phosphates but also medium-sized rings (Table 1, entries 4–8), including eight-membered ring where the corresponding triflates are known to be difficult to prepare.¹⁴ Since the seven-membered ketene acetal triflate decomposed even under these mild conditions,¹⁵ use of the phosphate leaving group is essential for this coupling reaction. The present method therefore appears to be quite general and efficient for synthesis of polycyclic ethers containing medium-sized rings.

The usefulness of the described method has been demonstrated in the concise synthesis of the ABCD ring system of CTX3C series (1, 2) (Scheme 1). Hydroboration of 5c with thexylborane proceeded regio- and stereoselectively to give, after oxidative workup, alcohol 6 in 73% yield (86% based on recovered 5c). Oxidation under Swern conditions followed by acidic treatment in MeOH effected removal of

the TBS and MOM groups and concomitant acetal formation giving hydroxy methyl acetal 7 in 82% overall yield. Further oxidation to the corresponding aldehyde followed by Wittig reaction provided terminal olefin 8 in 79% yield for the two steps. Reduction of 8 with $\text{Et}_3\text{SiH}-\text{BF}_3\cdot\text{OEt}_2$ proceeded smoothly to give tricyclic ether 9 as a single stereoisomer in 86% yield. Regioselective debenzoylation of 9 was carried out according to the method of Cipolla et al.¹⁶ to provide alcohol 10, which was allylated giving bisolefin 11 in 65% overall yield. Finally, ring-closing metathesis of 11 by using Grubbs' catalyst $[\text{RuCl}_2(\text{=CHPh})(\text{PCy}_3)_2]$ ¹⁷ furnished the desired ABCD ring system 12¹⁸ in quantitative yield. Thus, a concise and rapid synthesis of 12 was achieved in 10 steps and 30% overall yield from 3.

In conclusion, we have demonstrated Suzuki cross-coupling of alkylboranes with cyclic ketene acetal phosphates to be a powerful tool for the construction of polycyclic ethers containing medium-sized rings. The present methodology is thus believed to allow a general approach to convergent syntheses of polyether marine toxins. Further studies toward the total synthesis of ciguatoxins and their simplified analogues based on the present strategy are currently underway and will be reported in due course.

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Supporting Information Available: Synthetic schemes for compounds 3 and 4a–e, typical experimental procedures for synthesis of 4 and Suzuki cross-coupling reaction, spectroscopic data for compounds 5a–f, experimental procedures and spectroscopic data for compounds 6–12, and ^1H and ^{13}C NMR spectra for compound 12 (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(15) Reaction of the seven-membered ketene acetal triflate corresponding to 4c [aqueous 1 M NaHCO_3 (3 equiv), $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$ (0.05 equiv), Ph_3As (0.4 equiv), DMF, r.t. 20 h] gave 5c in only 29% yield.

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(18) The relative stereochemistry of 22 was firmly established by prominent NOEs between H-8/H-12, H-9/H-5 and H-9/H-11 (CTX3C numbering).